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IMMUNE-COMPLEX VASCULITIS: The Result of Paradoxical Deficits in Complement and IgG-Fc Receptor Functions

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Introduction. Vasculitis is a major component in the pathogenesis of rheumatic diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), and plays a fundamental role in the various types of glomerulonephritis. In addition, a number of serious multisystem diseases center on blood vessel inflammation including polyarteritis nodosa (PAN), Wegener's granulomatosis, Henoch-Schönlein purpura, temporal arteritis, Takayasu's arteritis and Behçet's disease. This diverse fabric of human illness shares a common thread in the form of elevated levels of circulating immune complexes which are abnormally deposited in blood vessel walls inducing inflammation, thrombosis, necrosis, and tissue injury.

This presentation will focus on recent discoveries of unexpected functions of serum complement and cellular complement receptors in the handling of immune complexes in man. Inherited and acquired defects of the complement cascade, and of the IgG-Fc receptor system may explain why some individuals develop vasculitis while others, in the presence of similar stimuli, do not. The potential role which these defects in the complement system play in the induction of autoimmunity is also fascinating. New diagnostic tests and new approaches to the therapy of the various forms of vasculitis will also be discussed.

OUTLINE

I. Clinical and pathologic classification of severe vasculitis
   A. Conditions with elevated immune complexes (IC)
   B. Infections, foods, drugs and unusual antigens in serum IC
   C. Clinical/serological features: PAN vs. rheumatoid vasculitis
   D. Clinical variations of Wegener's granulomatosis
   E. Glomerulonephritis as a specialized form of IC-vasculitis

II. Role of complement (C') in the processing of IC
   A. Inherited complement defects and the handling of IC
   B. Differential functions of C'receptors - CR1, CR2, CR3, CR4
   C. Limitation of size of forming IC - classical pathway
   D. Solubilization of insoluble IC - alternative pathway
   E. Modifying role of rheumatoid factors on complement function

III. Function of IgG-Fc receptors in the handling of IC
   A. FcR-I, 72 kD - high affinity, monomeric IgG, ag presentation
   B. FcR-II, 40 kD - large IC aggregates, activates endocytosis
   C. FcR-III, 50-70 kD - binds IC only for transport

IV. New tests for the diagnosis of active vasculitis
   A. A literature-based decision analysis model of PAN diagnosis
   B. Endothelial cell damage or clotting activation - Factor VIII related antigen, alkaline ribonuclease, plasma thrombospondin
   C. Deficits induced by vasculitis - tissue plasminogen activator
   D. Anti-neutrophil cytoplasmic antibody in Wegener's
   E. Use of EMG, selective angiography, MRI versus CT scans

V. Recent advances in the treatment of serious vasculitis
   A. Steroids: When, how much, and when not to use?
   B. Continuous oral, oral-pulse & IV cyclophosphamide + steroids
   C. Methotrexate and dapsone in cutaneous vasculitis
   D. Plasmapheresis + immunosuppression or anti-viral therapy

I. CLINICAL AND PATHOLOGICAL CLASSIFICATION OF SEVERE VASCULITIS

Since Dr. Pearl Zeek suggested that the biopsy was the gold standard for defining vasculitis (and it probably still is), blood vessel size and the type of cellular infiltrate around the damaged blood vessel have been the basis of classification for the systemic forms of vasculitis. Clinically, this approach has serious limitations because variations in blood vessel size and type of cellular infiltrate often occur within the same patient, requiring a clinical judgement in making the diagnosis. For example, some patients with polyarteritis nodosa (PAN) involving medium-sized muscular arteries serving large nerves (mononeuritis multiplex) may also have small arterioles and capillaries destroyed in the kidney (microscopic polyarteritis). Clinically the patient may show fever, leukocytosis, abdominal pain, hematuria, proteinuria, and hypertension, identical features to patients with classical PAN, yet be considerably less responsive to therapy than a patient whose kidney biopsy shows involvement of the larger arcuate arteries only. Thus, a kidney biopsy has to be factored into other clinical data in deciding diagnosis and prognosis. In Kawasaki's disease, the coronary arteries may show damage identical to adult PAN, but the mucocutaneous changes result from a leukocytoclastic vasculitis of the smallest arterioles and capillaries. In addition, severe (malignant) rheumatoid vasculitis shows blood vessel involvement similar to PAN, but many of the classical features of PAN are absent. Therefore, the clinical features must be an integral part of the classification, along with the biopsy result. Table 1 outlines a combined pathological/clinical classification of the serious forms of vasculitis.

TABLE 1. CLASSIFICATION OF THE SEVERE FORMS OF VASCULITIS

	(References)
Granulomatous Vasculitis:Large, Medium-sized Blood Vessels	
Temporal (Giant cell) arteritis	(1,2,3)
Granulomatous angiitis of the CNS	(1,3,4,5)
Takayasu's arteritis	(1,2,3,6)
Necrotizing Vasculitis:Medium-sized, Small Blood Vessels	
Classical polyarteritis nodosa (PAN)	(2,3,7,8,9)
Severe rheumatoid vasculitis (SRV)	(2,9,10)
Kawasaki's disease	(1)
Microscopic polyarteritis nodosa	(7)
Wegener's granulomatosis	(3,7,11,12)
Churg-Strauss syndrome	(7,8)
Behçet's syndrome	(1)
Hypersensitivity Vasculitis-Small Blood Vessels	
Leukocytoclastic (fragmented PMNs)	
Henoch-Schönlein purpura	(13,14)
Mixed cryoglobulinemia	(2,15,16)
Hypocomplementemia	(17,18,19)
Digital arteritis of RA	(15)
Systemic Lupus Erythematosus (SLE)	(13,14)

The cellular infiltrate in or around involved blood vessels ranges from almost 100% PMNs (PAN, leukocytoclastic vasculitides) to predominantly lymphocytes, macrophages and giant cells in the granulomatous forms of vasculitis (Wegener's, Churg-Strauss, and variants of giant cell arteritis). However, all of the forms of severe vasculitis listed in Table 1 may show elevated levels of circulating immune complexes (IC) in the blood. As shown in Table 2 a number of different diseases, infections or physiologic states can cause elevation of blood IC, yet most persons experiencing these conditions do <u>not</u> develop vasculitis. Why not? The amount and relative size, and what type of complement component the IC

contains are all important in determining the potential risk for developing vasculitis. Probably even more significant in this potential risk is the presence of certain inherited or acquired defects in the complement system and/or defects in the complement and IgG-Fc receptors on phagocytic (Kupffer) cells in the liver or on PMNs.

A. CONDITIONS WITH ELEVATED SERUM IMMUNE COMPLEXES

TABLE 2. DISEASES WITH INCREASED SERUM IMMUNE COMPLEXES (Ref. 20,21,22)

Rheumatic Diseases - RA, SLE, MCTD, AS, Scleroderma, PAN, Wegener's, Behçet's

Renal Disease - Glomerulonephritis

Infectious Diseases - SBE, Streptococcal, Gonococcal, Meningococcal, Leprosy, Syphilis, CMV, Hepatitis B, Dengue, EB virus, SSPE, Malaria, Trypanosomiasis, Shistosomiasis, Filariasis, Toxoplasmosis

Other - Psoriasis, Sarcoidosis, Eclampsia, TTP, Primary Biliary Cirrhosis, Intestinal By-pass, Inflammatory Bowel Diseases, after Vasectomy, Postprandial

B. INFECTIONS, FOODS, DRUGS AND UNUSUAL ANTIGENS IN SERUM IC

Recent studies of the serum IC or specific immunohistological staining of biopsies of vessel lesions in patients with vasculitis following known infections or drug exposure have linked microbial or drug-related antigens to blood vessel injury.

INFECTIONS AS A SOURCE OF FOREIGN ANTIGENS IN IC

For example, chronic pulmonary infections, which may elicit an IgA response in patients with cystic fibrosis have been associated with recurrent cutaneous vasculitis (palpable purpura) of the leukocytoclastic type with lesions which contain C3 and IgA when biopsied (Ref. 23). Group A streptococcal infections which cause acute glomerulonephritis have been shown to induce circulating IC containing extracellular antigens of the nephritogenic strains of group A streptococci, while serum IC from patients with rheumatic fever contain extracellular antigens from non-nephritogenic strains of streptococci (Ref. 24). Bacterial products elicit IC-associated leukocytoclastic vasculitis as shown following the therapeutic injection of various forms of streptokinase into patients after myocardial infarction (Ref. 25,26,27). The more intense the patient's immune response to the bacterial antigen, the more likely the induction of clinical vasculitis, as was noted in lepromin-positive patients with leprosy who develop erythema nodosum-like skin lesions (Ref. 28).

Of all infections, hepatitis B is most frequently associated with serious vasculitis (usually PAN, but occasionally the Churg-Strauss or leukocytoclastic types) (Ref. 29,30). Isolated reports of cutaneous vasculitis associated with cytomegalovirus (31), but not with human immunodeficiency virus (HIV) (Ref. 29) have been published.

FOOD ANTIGENS AS COMPONENTS OF IC

Carini (Ref. 32) has shown that patients with atopic eczema or asthma due to food antigens have serum IC containing a mixture of IgG(anti-IgE):IgE:food antigens in their circulation, and that even normal persons have circulating IC to ovalbumin and beta-lactoglobulin one to three hours after ingestion.

DRUGS AS ANTIGENIC COMPONENTS OF IC

Many drugs have been shown to cause necrotizing vasculitis (PAN, Churg-Strauss, Wegener's) or leukocytoclastic vasculitis. Penicillin (Ref. 33), over-the-counter medications such as phenylpropanolamine (Dexatrim) (Ref. 34), quinidine (Ref. 35), captopril (Ref. 36), propylthiouracil (Ref. 37), hydralazine (Apresoline) (Ref. 38), isoretinoin (Ref. 39) and cocaine (Ref. 40) have all been reported recently to have induced serious, life-threatening vasculitis.

UNUSUAL SOURCES OF ANTIGENS IN SERUM IC

Inflammatory bowel disease, and intestinal by-pass surgery, possibly by allowing the patient to absorb food and/or bacterial antigens, have also generated elevated levels of IC and, in the case of Crohn's disease, caused diffuse proliferative glomerulonephritis (Ref. 41) or in the case of ulcerative colitis, caused PAN (Ref. 42). Even hyposensitization therapy for non-seasonal rhinitis (against house dust, mixed grasses, alternaria, clodosporium, rhizopus, cephalosporium, fusarium and dust mites) has caused PAN (Ref. 43), and therapy for asthma (against grass pollen and house dust) has caused necrotizing vasculitis (Ref. 44).

C. CLINICAL/SEROLOGICAL FEATURES: PAN VS SEVERE RHEUMATOID VASCULITIS (SRV)

In the past, PAN and SRV, two of the most frequently encountered forms of severe vasculitis, have been considered essentially identical because of the marked similarity of pathological features when biopsied. However, closer examination of the clinical and serological features have shown significant differences, as summarized in Tables 3 and 4.

TABLE 3. COMPARISON OF CLINICAL FEATURES IN SEVERE RHEUMATOID VASCULITIS AND POLYARTERITIS NODOSA

Feature	SRV %	PAN %
Glomerulonephritis	34	75
GI Tract Vasculitis	67	67
bowel perforation	5	25
Arthritis	100	67
erosive changes on x-ray	98	<1
Fever	20	75
Weight Loss	53	99

From Bacon PA (Ref. 9)

TABLE 4. COMPARISON OF SEROLOGICAL FEATURES IN SEVERE RHEUMATOID VASCULITIS AND POLYARTERITIS NODOSA

Feature	SRV %	PAN %
IgM Rheumatoid Factor	97	38
IgG Rheumatoid Factor	95	9
Antinuclear antibodies	48	11
C1q-Immune Complexes (IC)	100	66
Platelet Aggregation IC	44	66
Anti-complementary activity IC	89	33
Cryoglobulins	96	40
Hepatitis B associated antigen	<5	36
Decreased C3-complement	0	21
Decreased C4-complement	67	25
Increased C3dg in serum	100	20

From Bacon (Ref. 9) and Geirsson, et al (Ref. 10)

D. CLINICAL VARIATIONS IN THE PRESENTATION OF WEGENER'S GRANULOMATOSIS

Several unpredicted clinical presentations have been observed in Wegener's granulomatosis. Rare eye involvement may be particularly resistant to cyclophosphamide, steroids and cyclosporin A (Ref. 45). Wegener's may involve the heart with acute pericardial tamponade (Ref. 46), or myocardial infarction and reversible aortic valvulitis (Ref. 47). Occasionally, the glomerulonephritis may precede the full-blown picture of sinusitis and pulmonary disease by two or more years (Ref. 48). And Wegener's granulomatosis may coexist with anti-glomerular basement membrane disease (Ref. 49) or present with massive pulmonary hemorrhage and capillaritis (Ref. 50), and thus be confused with Goodpasture's syndrome. As will be discussed below, the use of the new serum test for anti-neutrophil cytoplasmic antibodies may help resolve the diagnosis in favor of Wegener's in some of these unusual presentations of the disease.

E. GLOMERULONEPHRITIS AS A SPECIALIZED FORM OF IC VASCULITIS

TABLE 5. HUMAN IMMUNE COMPLEX GLOMERULONEPHRITIS

Type of Glomerulonephritis	Clinical Presentation	Granular Glomerular Deposits
Diff. prolifer.	Nephritis	Diffuse IgG, Variable IgA, IgM and C3
Crescentic prolifer.	RPGN*	As above, fibrin in cresc.
Focal or Mesangial prolifer.	Asymptomatic Prot./hematuria	Mesangial IgA, also IgG and/or IgM, C3
Membranous	Nephrotic Syndr.	Subepithelial IgG, C3
Membranoprolifer.	Nephritis/ Nephrotic Syndr.	Striking C3, type 2=little Ig*; type 1=IgG, IgA, IgM
End-stage changes	Azotemia	Variable Ig*, occ. 4+ C3
CTD* & systemic vasculitides	SLE, Henoch-Schönlein, Wegener's	Variable, SLE usually has 4+ IgG, IgA, IgM, C3, C1q

*RPGN = rapidly progressive GN, *Ig = immunoglobulin
*CTD = connective tissue diseases (Modified from Ref. 51,52,53)

Human IC-glomerulonephritis probably results from a misdirection of serum IC into the glomeruli or from a local interaction with kidney antigens (Ref. 51). Table 5 reviews some of the variations which occur in histological type, clinical presentation and the composition of the IC involved.

II. ROLE OF COMPLEMENT IN THE PROCESSING OF IC

The usual concept of the function of the serum complement system is linked to its potential to lyse antibody-sensitized cells or microorganisms, and to its enhancement of phagocytosis (opsonization). Thus, it was easy to visualize that complement played a role in the inflammation induced by IC in autoimmune diseases such as SLE and in other severe forms of vasculitis.

A. INHERITED COMPLEMENT DEFECTS AND THE HANDLING OF IC

However, although the serum complement system does play an important role in the production of inflammation, the unexpected occurrence of SLE-like disease and glomerulonephritis in the presence of genetic deficiencies of major complement components presented a seemingly paradoxical situation. Table 6 describes this surprising association.

TABLE 6. SLE AND GLOMERULONEPHRITIS ASSOCIATED WITH GENETIC DEFECTS OF COMPLEMENT

C1qrs	Complete absence gives a 90% risk of SLE, or IC-induced glomerulonephritis
C2	Complete absence of C2 gives a 50% risk of SLE.
C4A, C4B genes	Heterozygous null for one or the other in 35% of SLE patients, but in only 10% of "normal" Caucasians. Heterozygous null for both gives a 10-15% risk of SLE. Homozygous null for both (absent C4) gives a 90% risk.
Factor B	Inactivation prevented by C3 Nephritic Factor, an IgG autoantibody found in membranoproliferative glomerulonephritis, partial lipodystrophy and occasional patients with SLE
C3	Complete absence is associated with severe infections and IC glomerulonephritis, but <u>not</u> with an increased risk of SLE.

(Modified from Ref. 55-61)

There are several deductions which can be made from the above "experiments" of Nature. The total absence of C3 <u>prevents</u> SLE, suggesting that C3 plays a pivotal role in the inflammation and tissue injury of lupus. Since complete absence of any one of the classical complement pathway components (C1qrs, C2, C4) actually enhances the risk of developing SLE, this means that C3 has to be activated by the alternative complement pathway (Factor D, Factor B, C3b, Properdin). This alternative pathway activation of C3 leads to activation of terminal complement pathway components, C5,6,7, and C8,9, and contributes to the inflammatory component of SLE. This is not possible if C3 is genetically absent. Glomerulonephritis, on the other hand, can occur in the absence of either classical (C1qrs) or pivotal C3, suggesting that the IC involved are deposited in the kidney by some other mechanism, such as the IgG-Fc receptor on mesangial cells.

B. DIFFERENTIAL FUNCTIONS OF C' CELLULAR RECEPTORS CR1, CR2, CR3, CR4

Fortunately, the discovery by Fearon, et al, (Ref. 55,62,63,64) of the receptor for C3b/C4b on the human erythrocyte provided a better explanation for the mechanism of vasculitis when early components (C1qrs, C4, or C2) of the classical pathway were missing. This receptor which is now referred to as complement receptor type 1 (CR1) provides the bulk of the binding potential for IC in the blood. Later, three other cellular receptors for degradation products of C3b (iC3b, C3dg, C3d) were identified and are also shown in Table 7 below.

TABLE 7. RECEPTORS AND OTHER FACTORS WHICH REGULATE COMPLEMENT ACTIVATION AND INACTIVATION

CR1	Binds C3b/C4b:IC and transports IC to the liver; Degrades C3b to iC3b
CR3 & CR4	Binds iC3b (& fibrinogen) to PMNs and to macrophages in liver and spleen
CR2	Binds C3dg (& EB virus), presents ag to T & B cell afferent arm of immune response
Factors H&I	With CR1, degrade C3b to iC3b
Factor I	With CR1 degrades iC3b to C3dg
Decay-accelerating Factor (DAF)	Degrades C3 convertase (C42) complex and 3 convertase of the alt. pathway
C4 binding protein	Enhances degradation of C4b

Just how significant CR1 is for IC binding and transport was shown in fascinating experiments performed in baboons by Hebert and his colleagues (Ref. 65,66,67), summarized in Figure 1. They injected 125-Iodine tagged C3b-coated IC intravenously, and showed that within 60 seconds 80% of the 125-Iodine labeled IC became bound to formed elements in the blood with over 60% bound to red blood cells. However, with the first passage through the liver, 95% of the labeled IC were removed, suggesting that in the presence of normal serum complement levels, the liver was the major site of removal of IC. However, when the baboons were depleted of complement, the IC were cleared more rapidly,but now not by the liver and spleen (Ref. 66). Rather the IC were distributed throughout the body, particularly to peripheral blood vessels and the kidneys, thus providing the potential for IC-mediated tissue injury. Distribution to lymph nodes and bone marrow also provided the potential stimulus for an enhanced immunological response to the antigen component in the IC above that which would have occurred if the IC had been taken up by liver Kupffer cells and degraded.

These and other experiments (Ref. 68,69,70) have shown that C3b and and C4b bind to IC and provide the hook by which IC are picked up in the blood, mostly by the CR1 on red blood cells, then transported to the liver where IC can be transferred to CR3 receptors on Kupffer cells and endocytosed. Since C1qrs and C2 must first be activated before C4 and C3 can be bound to the IC, the absence of any one of the early classical complement pathway components impairs this normal transport mechanism, leaves the IC free in the serum and exposes non-hepatic tissues to a high concentration of large IC.

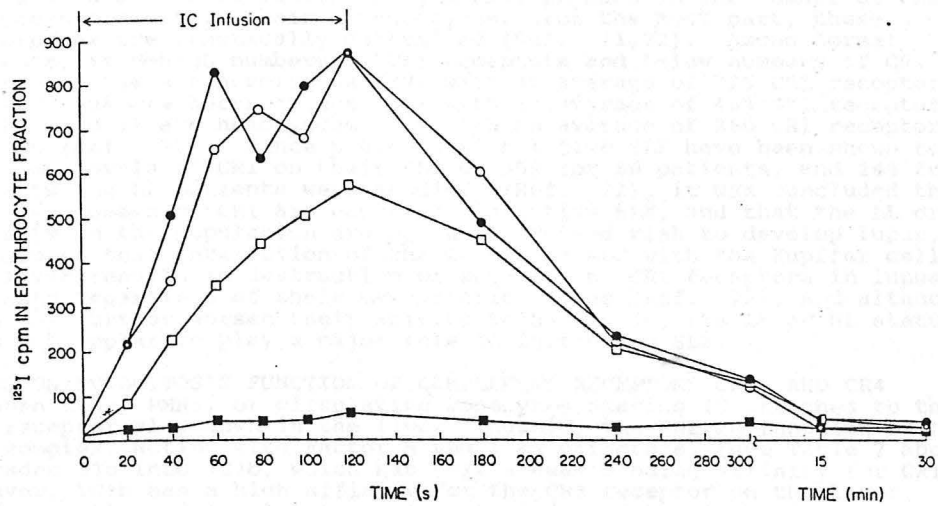

FIGURE 1.
Sequential changes in counts per minute of 125-I in RBC fractions of blood samples drawn simultaneously from an artery (●), renal vein (○), portal vein (□), and hepatic vein (■) during and after infusion of 125-I-labeled IC. Note that the IC are removed from the RBC's in the liver, but not in the kidney. (Ref. 65).

MOLECULAR STRUCTURE OF COMPLEMENT RECEPTOR TYPE 1 (CR1)

Fearon and his colleagues (Ref. 55, 64) have determined the molecular structure of the human CR1 receptor of the erythrocyte. This is diagramatically presented in Figure 2 below. Each sphere represents a distinct polypeptide unit. Each group of seven identical units makes up what is known as a Long Homologous Repeat (LHR). The most peripheral of these, LHR-A, binds C4b, the next two, LHR-B and LHR-C, bind C3b, and the most interior, LHR-D binds neither. All four LHR's attach to two polypeptide units linked to the cell membrane. In the case of the RBC, this receptor is located in a membrane pit, not unlike the cholesterol receptor on the liver parenchymal cell.

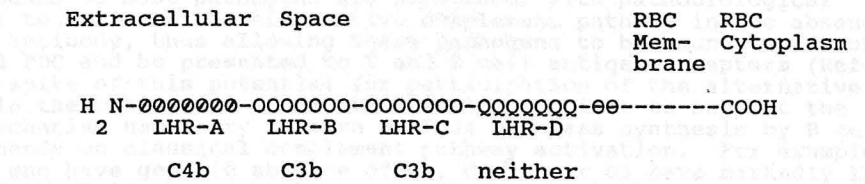

FIGURE 2. COMPLEMENT RECEPTOR TYPE 1 (CR1) ON THE ERYTHROCYTE
LHR = Long Homologous Repeats, each made of 7 similar polypeptide units. Two combining sites for C3b and one for C4b magnify the CR1 binding affinity for C3b/C4b-containing IC. (Ref. 55,64).

GENETIC AND ACQUIRED DIFFERENCES IN THE NUMBER OF CR1 PER RBC

There is a wide variation among normal persons in the number of CR1 receptors present on their erythrocytes. For the most part, these differences are genetically determined (Ref. 71,72). Among normal subjects, if H=high numbers of CR1 receptors and L=low numbers of CR1 receptors, 54% are homozygous (HH) with an average of 725 CR1 receptors per RBC, 39% are heterozygous (HL) with an average of 463 CR1 receptors per RBC and 7% are homozygous (LL) with an average of 260 CR1 receptors per RBC (Ref. 72). Since patients with active SLE have been shown to have low levels of CR1 on their RBC's, 359 for HH patients, and 263 for HL patients (no LL patients were studied) (Ref. 72), it was concluded that acquired losses of CR1 are occurring in active SLE, and that the LL or HL variants in the population are not at increased risk to develop lupus. It is assumed that interaction of the IC-coated RBC with the Kupffer cell in the liver results in destruction of some of the CR1 receptors in lupus patients regardless of their CR1-genetic status (Ref. 72), and although this may further worsen their ability to handle IC, the LL or HL status does not appear to play a major role in initiating SLE.

ADHESION/ENDOCYTOSIS FUNCTION OF COMPLEMENT RECEPTORS CR3, AND CR4

When RBCs, PMNs, or circulating monocytes bearing IC attached to the CR1 receptor slow down in the liver sinusoid, the enzyme function of the CR1 complex, acting with Factor H and I as cofactors, (see Table 7 above) degrades C3b into iC3b, which has only a weak binding affinity for CR1. However, iC3b has a high affinity for the CR3 receptor on the liver Kupffer cell, and an almost complete transfer of the iC3b-IC to liver phagocytic cells occur. The CR3 receptor is a surface glycoprotein composed of an alpha chain (165 kD) and a beta chain (95 kD), and has the potential to activate the phagocytic cell to endocytose the IC and degrade them (Ref. 73). The CR3 receptor also has the potential to recognize fibrinogen (Ref. 73), and to promote adhesion of PMNs to vascular endothelium and to each other (Ref. 74). A similar receptor, designated CR4, with only minor differences in its alpha chain (150 kD), has a similar affinity for iC3b and is also found on PMNs and on peripheral blood monocytes (Ref. 75).

IMMUNOREGULATION BY IC BOUND TO CR2 ON B CELLS AND FOLLICULAR DENDRITIC CELLS

In contrast to CR1, utilized primarily for transport of IC, and CR3 and CR4, utilized for endocytosis of IC by phagocytic cells and for enhancement of endothelial adhesion or self-aggregation of PMNs and monocytes, CR2 plays an immunoregulatory role in the afferent arm of the immune response (Ref. 76,77,78). CR2 is a single glycosylated peptide chain with a molecular weight of 145 kD which interacts preferentially with the terminal activation/processing fragments of C3 (C3dg, and C3d). CR2 is located on B lymphocytes and on the dendritic cells in the lymphoid follicle (Follicular Dendritic Cells = FDC).

C3dg and C3d remain covalently bound to most IC. In addition, C3dg and C3d are bound to most pathogens and substances with pathobiological potential to activate the alternative complement pathway in the absence of specific antibody, thus allowing these pathogens to be bound to CR2 on B cells and FDC and be presented to T and B cell antigen receptors (Ref. 76). In spite of this potential for participation of the alternative pathway in the activation of C3, this is insufficient to support the switch mechanism necessary to turn on IgG4 subclass synthesis by B cells, which depends on classical complement pathway activation. For example, patients who have genetic absence of C1, C4, C2 or C3 have markedly lower levels of the IgG4 than normal persons (Ref. 79). IgG4 reacts preferentially with certain food, parasitic and insect-derived antigens (such as bee venom).

These antigens which elicit an IgG4 response are T-cell-dependent, and thus CR2-linked IC may be required for the switch to IgG4 synthesis. IC bound to CR2 on B cells also co-cap specific Ig receptors to facilitate the anamnestic or B lymphocyte memory response (Ref. 80).

The decay-accelerating factor (DAF)(see Table 7 above) is a T cell surface phosphotidylinositol-linked protein of 70 kD molecular weight which binds to C3b, C4b, and the C3 convertase of the alternative pathway. DAF has also recently been shown to cause T cell proliferation when activated (Ref. 81). A second component of CR2 which contains the binding site for the Epstein-Barr virus can generate polyclonal B lymphocyte activation (Ref. 76,77) including autoantibody formation (Ref. 55,57).

C. LIMITATION OF IC-SIZE WHEN FORMED IN THE PRESENCE CLASSICAL PATHWAY

Yet another function of the early complement pathway components impacts on the processing of IC. Nussenzweig and his colleagues (Ref. 82,83), and later Schifferli, et al (Ref. 68) showed that IC formed in the presence of an intact classical complement pathway are much smaller that those formed in the absence of complement, and that a heavy coating of C3b which decreases the size of the lattice of the IC is responsible for this change. Since smaller IC are less damaging and more rapidly destroyed, the absence of C1qrs, C4 or C2 allows larger IC to form, and these larger IC are more likely to cause vasculitis. Because IgA-IC do not activate the classical complement pathway, IgA-containing IC contain much less C3b, bind poorly to CR1, are cleared more slowly than IgG-containing IC, and are preferentially deposited in renal glomeruli (Ref. 67).

D. SOLUBILIZATION OF INSOLUBLE IC BY ALTERNATIVE PATHWAY COMPONENTS

Already formed IC, both of IgA and IgG type can be solubilized by the alternative pathway (Ref. 84,85). This may well explain the problem of accelerating glomerulonephritis which occurs in some SLE patients with very low C3 levels, and the excellent correlation with clinical improvement that accompanies steroid or immunosuppressive therapy which succeeds in restoring C3 to its normal range.

E. MODIFYING ROLE OF RHEUMATOID FACTORS ON COMPLEMENT FUNCTIONS

There is a substantial defect in IC solubilization in SLE, nephritis, and vasculitis (Ref. 86) as well as in RA (Ref. 87,88). The decrease of IC-solubilization capacity is correlated with the decrease of hemolytic activity of the alternative complement pathway and with higher levels of immune complexes in the sera tested (Ref. 88), as well as with high serum levels of both IgM and IgA rheumatoid factors (Ref. 85,87,88). This acquired defect of complement function which impairs normal handling of IC might explain the IC-vasculitis seen in many of the extraarticular features of RA such as epicleritis, nodule formation, digital arteritis and rarely, malignant rheumatoid vasculitis (Ref. 89,90). However, in RA, unlike SLE, the risk of vasculitis is not increased by the genetic absence of major complement components (Ref. 57).

III. FUNCTION OF IgG-Fc RECEPTORS IN THE HANDLING OF IC

Haakenstad and Mannik (Ref. 91) showed that saturation of the reticuloendothelial system (RES) by overloading it with soluble IC delayed the clearance of IC from the circulation, and led to their subsequent deposition in tissues. Recently when Daha, et al, (Ref. 92) incubated large soluble aggregates of IgG (~32,000,000 mol wt) in vitro (in the absence of serum complement) with optimum numbers of peripheral blood monocytes from normal individuals, 9.8% of the soluble aggregates were taken up and degraded. When a similar study was done in the presence of complement, 27% of the soluble aggregates were taken up and degraded. This indicated that, under the in vitro conditions studied, that 36.3% (9.8/27) of the uptake could be attributed to the IgG-Fc receptors on the monocytes and suggested that a substantial proportion of IC handling in normal subjects was by the IgG-Fc receptor system (Ref. 92). This same study examined monocytes from clinically active RA patients with and without vasculitis, and found that both groups of RA patients had monocytes which showed a significantly lower degradation of IgG aggregates, both with and without added complement. This study suggested that acquired defects in Fc-receptor function may play a role in the build-up of IC in the serum of patients with active RA, and thus contribute to the pathogenesis of vasculitis. However, the above observation (Ref. 61) that patients with a total absence of C3, and thus non-functional CR1, CR2 and CR3 receptors, still develop IC glomerulonephritis, emphasizes the inadequacy of the IgG-Fc receptor system in the appropriate handling of IC.

Recently, more detailed study of the IgG-Fc receptor system has revealed that at least three receptors with distinctly different cellular distribution and functional potential are present (Ref. 93,94,95). See Table 8 and Table 9 below. The FcRI receptor is of particular interest in that 4 members of a family have been shown to be genetically totally deficient in FcRI. Monocytes from this family have been shown to be unable to activate their T lymphocytes in the presence of mIgG2b anti-CD3, a mouse monoclonal antibody which requires the FcRI receptor on the macrophage for binding. This suggests that the FcRI receptor may play an important role in antigen presentation to T lymphocytes when the antigen is in an IC (Ref. 93). Another Fc-receptor, FcRIII, is PMN-elastase sensitive (Ref. 94), and shares with the IgG and IgA molecules in IC the potential for inactivation in chronic inflammatory foci rich in PMNs.

TABLE 8. THREE DIFFERENT TYPES OF IgG-Fc RECEPTORS

Receptor	Detected by Mouse mAb	Status of Fc Bound	Found on which cells
FcRI 72kD,High Affinity	32.2,44.1	Monomeric HuIgG1&3, MouseIgG3 & mIgG2a	Mono, and Macro PMN after 18 h r-InF
FcRII (1X) 40 kD,Low Affinity, Activates	IV.3 (CDw32)	Aggregated Hu IgG, MouseIgG1 & mIgG2b	PMN, Mono, Platelet, B-cells
FcRIII (7X) 50-70 kD Binds only	3G8,NKP.15, Leu 11a	Elastase sensitive	Macro, PMN, Eos,T-gamma NK cells

Ceuppens, et al; Tosi & Berger (Ref. 93,94)

PMN-elastase destroys the hinge region of the Fc of IgG and IgA and makes IC containing IgG and IgA unable to bind to cellular Fc receptors (Ref. 96). Thus PMN-elastase may act to suppress phagocytic cell-mediated inflammation in chronic conditions such as cystic fibrosis, but it may also delay appropriate handling of IC and lead to vasculitis (Ref. 23).

TABLE 9. ROLE OF IgG-Fc RECEPTORS IN INFLAMMATION

Immune complex binding (FcRII, FcRIII)
Internalization of IgG-coated cells, bacteria and other immune complexes (FcRII)
Metabolic activation of phagocytic cells (chemiluminescence, superoxide production, degranulation) (FcRII)
Antibody-dependent cytotoxicity (FcRII)
Ag presentation (Macrophage to T-cell) (FcRI)

Ceuppens, et al; Tosi & Berger (Ref. 93,94)

IV. NEW TESTS FOR THE DIAGNOSIS OF ACTIVE VASCULITIS

Not infrequently, active vasculitis involves blood vessels in internal organs such as the liver, GI tract, lungs, brain or kidneys, and presents initially as a confusing illness with fever, abdominal pain, anorexia, weight loss, vague malaise, leukocytosis and elevated ESR. In the absence of visible vasculitic skin lesions, early diagnosis of serious vasculitis may be difficult. Using published information about PAN, Albert and his colleagues have developed a decision analysis model for the diagnosis of PAN (Ref. 97) which they have empirically tested and shown to be useful (Ref. 98).

Even when vasculitis is suspected, the contemplation of the substantial risk of doing a biopsy of an internal organ such as the kidney or liver should make any physician cautious: The sicker the patient, the bigger the risk! For this reason, the recent development of new blood tests for evidence of active blood vessel injury should prove particularly valuable. One of these tests, the serum Factor VIII-related antigen level (Ref. 99,100), helps to differentiate the medium and large vessel types of necrotizing vasculitis from small vessel disease, see Table 10. Three other blood tests, the alkaline ribonuclease level (Ref. 101), see Table 11; the plasma thrombospondin level (Ref. 102), see Table 12; and the release of tissue plasminogen activator (Ref.103) after 5 minutes of venous occlusion with a blood pressure cuff also promise to be of potential value. None of these first four tests are, as yet, readily available. However, another, the serum anti-neutrophil cytoplasmic antibody level (Refs. 104-113) has already become commercially available, and promises to be a highly specific, sensitive assay for Wegener's granulomatosis. Anti-neutrophil cytoplasmic antibody is present in 90% of patients with Wegener's granulomatosis, and was not found in 200 control patients with PAN, RA, SLE, MCTD, etc. (Ref. 104). This new test also provides a disease activity index with which to follow the patient's response to treatment (Ref. 105,110).

TABLE 10. FACTOR VIII-RELATED ANTIGEN IN VASCULITIS

Factor VIII-related Antigen - a marker of endothelial cell injury is raised 2 to 7-fold in systemic necrotizing vasculitis (PAN, Wegener's, Severe Rheumatoid Vasculitis) but not in small vessel cutaneous vasculitis. It falls with response to therapy.
Woolf, et al (Ref. 99) & Belch, et al (Ref.100)

TABLE 11. SERUM ALKALINE RIBONUCLEASE IN VASCULITIS

Alkaline Ribonuclease - a marker of endothelial cell injury rises 2-fold in severe rheumatoid vasculitis. It is not significantly elevated in the serum of RA patients without severe vasculitis, but it may be elevated 4.5-fold above normal in serum from renal failure patients. Serum from severe rheumatoid vasculitis causes a release from cultured endothelial cells of 3-fold more alkaline ribonuclease than that released in the presence of the same amount of normal serum, suggesting direct toxicity of a serum component (immune complexes?).
From Oribe, et al (Ref. 101)

TABLE 12. PLASMA THROMBOSPONDIN LEVELS IN VASCULITIS

Plasma Thrombospondin - A 420 kD glycoprotein found in the secretory granules of human platelets, and shown to be synthesized in megakaryocytes, vascular endothelial cells, fibroblasts, monocytes, and smooth muscle cells, is elevated an average of 13-fold in the plasma of children with a variety of forms of vasculitis (PAN, Kawasaki's, SLE, dermatomyositis, non-specific vasculitis) over the levels found in patient controls without vasculitis (791±1412 vs 59±29 ng/ml). A positive correlation with the level of fibrin degradation products was also noted.
From McCrohan, et al (Ref. 102)

Somewhat more invasive tests may give valuable clinical information in helping diagnose vasculitis. For example, bronchoalveolar lavage in patients with active Wegener's reveals a prominence of T lymphocytes in the bronchoalveolar space with a suprisingly high level of CD8 positive (cytotoxic or suppressor) T cells (Ref. 114). This emphasizes the prominent role of T-cell mediated inflammatory responses in the granulomatous variants of necrotizing vasculitis such as Wegener's.

EMG and nerve conduction studies are particularly valuable in the diagnosis and follow-up of systemic forms of vasculitis. In a study of 22 patients (16 with PAN and 6 with a Churg-Strauss syndrome), 9 presented clinically with mononeuropathy or mononeuropathy multiplex characteristic

of ischemic injury to a peripheral nerve (Ref. 115). Nine others presented with a more diffuse neuropathy and the remaining 4 developed neuropathy during the course of their disease (Ref. 115). Usually the EMG examination revealed more diffuse neuropathy than would have been predicted from clinical symptoms.

Prior to considering a potentially dangerous biopsy of the kidney or liver, selected angiography should be performed. In a study of 26 patients with PAN, all of whom underwent angiography, 15 were shown to have aneurysms (Ref. 116). The presence of aneurysms correlated best with patients with clinically severe disease, severe hypertension and the presence of hepatitis B surface antigen (50% of the 8 tested with aneurysms compared to none of 9 tested in the patients without demonstrable aneurysms at the time of angiography). Cerebral angiography can also be a valuable test in patients suspected of having central nervous system vasculitis (Ref. 117). Angiography has the advantage of the large number of vessels which can be evaluated at one time, avoiding selection error when the vasculitis shows focal areas of involvement.

Magnetic resonance imaging (MRI) has been shown to be a sensitive method to detect clinically silent or symptomatic vasculitic lesions of the brain (Ref. 118) although the most frequent abnormality found (50% of patients), periventricular plaques in the cerebral white matter, was similar to the lesions found in multiple sclerosis. MRI detected more lesions than could be seen on computed tomography (CT) scans of the same patients, and in no case were lesions seen on CT and not present on the MRI scan. Although CT scans show brain atrophy secondary to vasculitic injury well (Ref. 119), MRI is more sensitive and is the preferred test for cerebral vasculitis (Ref. 118).

V. RECENT ADVANCES IN THE TREATMENT OF SERIOUS VASCULITIS

The life-threatening aspects of PAN and Wegener's are well known to the clinician. If completely untreated, only 12% survive 5 years, and more than 30% die within the first 6 months of their disease. High doses of steroids in PAN only increases this 5 year survival to 48% of patients, and may not increase survival at all in patients with Wegener's granulomatosis. This has led to an agonizing reappraisal of the various forms of treatment. This presentation will focus on four recent advances which prolong survival and prevent morbidity in serious vasculitis.

A. STEROIDS: WHEN, HOW MUCH AND WHEN NOT TO USE?

Some minor forms of vasculitis, such as erythema nodosum, and some major allergic types of vasculitis such as erythema multiforme bullosum (Stevens Johnson Syndrome) respond dramatically to modest doses of prednisone, 15-40 mg/day. The same can be said for most patients with giant cell arteritis (temporal arteritis, Takayasu's arteritis) with most patients responding dramatically to 40-60 mg of prednisone/day within 7-14 days, and then capable of being maintained in reasonable remission on 7.5-15 mg/day for the duration of their disease (usually 6-24 months).

The allergic angiitis of Churg-Strauss syndrome is more resistant, but also usually responds to steroids alone. Occasionally pulse methylprednisolone therapy 1 gram/day for 3 to 4 days is necessary to begin a remission (Ref. 120), and maintenance steroids or cy clophosphamide may be required to prevent relapse. The eosinophil count is a valid and useful means of determining the adequacy of the steroid dosage when tapering steroids in the Churg-Strauss syndrome (Ref. 121). It is more and more evident that long-term, or high dosage steroid therapy carries a major threat of morbidity (infections, aseptic necrosis of bones, steroid-induced osteoporosis, obesity, diabetes, hypertension, glaucoma, and personality changes).

A recent evaluation of pulse methylprednisolone use in polyarteritis involving the kidney showed its use to correlate with decreased one year survival (Ref. 122). In general, leukocytoclastic forms of vasculitis are poorly responsive to steroid therapy, and when treatment is necessary, steroids should be used in conjunction with immunosuppressive therapy.

B. CONTINUOUS ORAL, ORAL-PULSE, AND IV CYCLOPHOSPHAMIDE + STEROIDS

Most studies have shown the alkylating agents such as cyclophosphamide to be far more effective in arresting the tissue injury associated with PAN or Wegener's than other agents, and the simultaneous administration of modest doses of prednisone has usually given less morbidity and better acceptance of the therapy (Refs. 9,123-128). Table 13 reviews the experience of Bacon and his colleagues in England with the various dosage schedules using cyclophosphamide and steroids (Ref. 9,122) to treat PAN, Wegener's granulomatosis, and severe rheumatoid vasculitis.

TABLE 13. CONTINUOUS VERSUS INTERMITTENT USE OF CYCLOPHOSPHAMIDE/STEROID REGIMES FOR RHEUMATOID VASCULITIS AND PAN/WEGENERS

Drug Regimen	Number of Pts. SRV	PAN/Weg	Death %	Relapse %
Continuous oral Cyclo 2-2.5 mg per kg + Pred	4	21	23	31
IV Cyclo 15 mg per kg q 3 wk + IV Me Pred	29	15	20	11
Oral Cyclo 5mg per kg X3 days every 2-3 wks + oral Pred	10	15	12	9

From Bacon PA, et al (Ref. 9,122)

The above experience with Wegener's granulomatosis has been confirmed by others (Ref. 127,128). However, morbidity associated with cyclophosphamide use is substantial. When the WBC is maintained above 3,000/cu mm, infections are minimized (Ref. 127). H. zoster is seen in 10-20% of patients, 15% develop hemorrhagic cystitis (Ref. 128), and most patients are sterilized if cyclophosphamide is used for over one year. In Fauci and Wolff's 85 patients followed at NIH for up to 21 years, only one developed a lymphoproliferative neoplasm. This is low when compared to the approximately 10% risk of lymphoproliferative neoplasia in rheumatoid arthritis patients who received cyclophosphamide for a six year period. It may well reflect the remission which can be induced in most patients with Wegener's patients which allows termination of the cyclophosphamide after an average of one year of treatment (Ref. 127). About 7% of Wegener's patients fail to respond to cyclophosphamide and steroids. Three such patients have been successfully treated with cyclosporin A (Ref. 129,130).

A surprising new development in the treatment of Wegener's granulomatosis with trimethoprim/sulfamethoxazole has recently been reported (Ref. 131,132,133,134). Because of the proven success of cyclophosphamide therapy in Wegener's, caution has been expressed about hasty acceptance of trimethoprim/sulfamethoxazole therapy (Ref. 132).

Nevertheless, if valid, the possibility of an infectious accompaniment (?Staphylococcus aureus) providing the antigenic stimulus for Wegener's needs to be strongly considered.

C. METHOTREXATE AND DAPSONE IN THE THERAPY OF CUTANEOUS VASCULITIS.

Safer therapeutic agents are needed to manage chronic forms of vasculitis where long-term steroids or alkylating agents pose serious potential toxicity. Low-dose methotrexate therapy has been used successfully to treat the cutaneous vasculitis associated with RA (Ref. 135). When it was stopped, the vasculitis recurred, and again remitted when methotrexate was restarted. Except for minor liver fibrosis (seen in 48% of patients after 1.5-1.0 g total dose), methotrexate is proving safer than long-term steroids. Dapsone, 100-150 mg/day is another alternative in the management of leukocytoclastic vasculitis (Ref. 136), or leg ulcerations related to vasculitis in the rheumatoid patient (Ref. 137). Although used in the therapy of leprosy, the action of sulfones in vasculitis is unclear. They have been shown to suppress oxygen-derived free radical formation in PMNs and to inhibit prostaglandin PGD2 in rat mast cells (Ref. 137).

D. PLASMAPHERESIS + IMMUNOSUPPRESSION OR ANTI-VIRAL THERAPY

Many patients (perhaps 20-30%) of patients with severe PAN present with advanced vascular injury to renal or abdominal vessels. In some, the progression of the PAN is so rapid that the lag in onset of immunosuppression may cost them their lives. For this reason, use of plasmapheresis along with cyclophosphamide has been needed to remove the circulating IC to stop the rapid progression of their disease (Ref. 138), and in those patients in whom the offending antigen is Hepatitis B surface antigen, simultaneous treatment with long-term immunosuppression or with an anti-viral agent such as adenine arabinoside (Vidaribine) may be helpful (Ref. 139). As noted above it is the Hepatitis B-associated PAN which tends to be more severe and to produce widespread vascular aneurysms (Ref. 116).

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